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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,873	09/05/2003	Shyam S. Mohapatra	USF-182XC1	6872

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EXAMINER

LIETO, LOUIS D

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 12/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/655,873	Applicant(s) MOHAPATRA ET AL.	
	Examiner Louis D. Lieto	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 July 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 6-9, 11, 12, 14, 15, 18-21, 23-31 and 43-57 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6-9, 11, 12, 14, 15, 18-21, 23-31 and 43-57 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s), including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input checked="" type="checkbox"/> Other: <u>Vector Map</u> . |

DETAILED ACTION

The previous Office Action mailed on 10-17-2005 is withdrawn. The Office Action attached below is submitted as a replacement. Please note that duplicate references have not been included with this office action.

Applicant's response filed on 7/15/2005 is acknowledged. Claims 1-4,6-9,11,12,14,15,18-21,23-31,43-57 are pending in the instant application. Applicant amended claims 1-4,6-9,11,12,18,20,21 and 23-29, canceled claims 5,10,13,16-17,22 and 32-42, and added new claims 43-57. The sections of title 35 U.S.C not included in this office action can be found in a previous office action. An action on the merits follows.

Priority

The objection over failure of the applicant to refer to provisional Application No. 60/319,523 in the beginning of the specification is withdrawn in view of applicant's arguments that such statement was in fact present.

Specification

The objection to the specification for containing informalities is withdrawn in view of applicant's amendment to the specification.

Claim Rejections - 35 USC § 112

The rejection of claims 1-15, 18-31 and 34-39 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicant's

amendments to the claims.

The rejection of claims 1-15, 18-31 and 34-39 under 35 U.S.C. 112, first paragraph, for lack of full scope of enablement is withdrawn in view of applicant's arguments and amendments to the claims.

Rejections under second paragraph of 35 U.S.C. 112:

The rejection of claims 1-15, 18-31 and 34-39 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of applicant's arguments

Claim Rejections - 35 USC § 103

The rejection of claims 1-10, 12-14, 20-29, 34-36, 38, and 39 under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. {Hogan et al. (1998) Eur. J. Immunol. 28: 413-423}, and further in view of Li et al. {Li. et al. (1996) J. Immunol. 157: 3216-3219} and Carroll et al. {Carroll et al. (1998) J. of the Nat. Canc. Inst. 90:1881-1887} is withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 4,9,11,14,15,18, 20, 27,28,30,31,43-48,51-56 are newly rejected under 35

U.S.C. 102(a) as being anticipated by Kumar et al. {Kumar et al. (2001) J. Allergy Clin Immunol; 108:402-8}. This new rejection is necessitated by applicant's amendments to the claims.

Applicant should note that the inventors of the present application authored the reference of Kumar et al., however Aruna K. Behera, Jianan Hu and Richard F. Lockey, who are not listed as inventors on the instant application, also authored the reference of Kumar et al.

Kumar et al. provides guidance on the administration of plasmids encoding the cytokines IL-12 and IFN- γ (Abstract). Wherein one plasmid encodes both the mouse p35 subunit and the mouse p40 subunit, each under the control of a separate CMV promoter and the second plasmid encodes mouse IFN- γ (pg. 403, col.1). Kumar et al. teaches that the plasmids are administered together via intramuscular injection to the mice, along with a subcutaneous injection of Kentucky bluegrass extract. Wherein, mice vaccinated with the plasmids had lower levels of IgE and higher levels of grass allergen specific IgG2a in comparison with control mice (Abstract). Further, Kumar et al. teaches that the vaccination with the plasmids increased the production of TH-1 type cytokines, such as IL-2, and decreased production of IL-4 cytokines such as IL-4 (Abstract; pg. 405, Figure 3). These changes prevented the development of airway hyper-responsiveness (pg. 405, col 2). Finally, Kumar et al. teaches that delivering plasmids encoding IL-12 and IFN- γ together is more effective at inducing a protective airway response than delivering them alone.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Original, amended or new claims 1-10, 12-14, 20-29, 43-45, 47, 49, 50, and 54-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. {Hogan et al. (1998) Eur. J. Immunol. 28: 413-423}, and further in view of Li et al. {Li et al. (1996) J. Immunol. 157: 3216-3219} and US patent 6,693,086 (2.17.2004) priority to (6.25.1998), hereafter referred to as Dow et al. This new rejection is necessitated by applicant's amendments to the claims.

Hogan et al teaches the construction and administration of a vaccinia virus encoding the p35 subunit and the p40 subunit of mouse IL-12 operably linked to a promoter (pg. 420, Section 4.7). Said sequences are biologically equivalent to SEQ ID NOs: 7 & 8 (human p35 subunit) and SEQ ID Nos: 9 & 10 (human p40 subunit). Further, Hogan teaches that in mice sensitized with OVA (pg. 420, Section 4.2), IL-12 gene delivery inhibits airway inflammation (pg. 415, Figure 1, Col. 1), increases the levels of IFN- γ (Th-1 type cytokine) and decreases the levels of IL-4 and IL-5 (Th-2 type cytokines) expressed in lung cells (pg. 416, Figure 2) after intranasal administration in gelatin saline (pg. 420, Section 4.7). Hogan et al. teaches that IL-12 protects against lung damage by increasing the levels of IFN- γ expressed (pg. 418, col.1). Finally, Hogan

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et al teaches that viral titers in the mouse lung peaked at day 3 after administration of vaccinia encoded IL-12 (pg. 417, Figure 4), which indicates that the viral nucleic acid was contained within a cell. Hogan et al. does not teach the administration of IFN- γ encoded within the same vaccinia virus.

Li et al. supplements Hogan et al. by providing guidance on the construction of a plasmid vector encoding IFN- γ and operably linked to a promoter; followed by administration of the vector to mice suspended in lipofectamine (pg. 3216, Col. 1, Materials and Methods). Said plasmid encoded IFN- γ is biologically equivalent to SEQ ID NOs: 11 & 12 (human IFN- γ). Li et al. shows that the IFN- γ is expressed in higher levels of treated mice and that the vector is contained within mouse lung cells (pg. 3217, Figure 1). Finally, Li et al shows that administration of vector encoded IFN- γ inhibits pulmonary allergic responses in mice sensitized with CA (pg. 3217 col. 1) and leads to a significant decrease in eosinophilia (pg. 3218, Figure 2, Col 2.).

Dow et al. supplements Hogan et al. by providing guidance on a method for systemic immune activation for protecting a mammal from a disease associated with allergic inflammation (Abstract). Dow et al. teaches that eliciting an immune response that alters the overall immune response in a mammal can be particularly effective in the treatment of allergic inflammation (col. 14, lines 40-65). For example, elicitation of a Th1-type response in a mammal that is undergoing a Th2-type response. Th2-type T lymphocytes can be characterized by their production of one or more cytokines, collectively known as Th2-type cytokines, such as interleukin-4 (IL-4) or interleukin-5 (IL-5) (col. 14, lines 40-65). Dow et al. teaches the administration of expression vectors using pCR3.1, which encode IL-12 or IFN- γ , via

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liposomes, to mice (col. 37, lines 1-60). The pCR3.1 vector from Invitrogen has a CMV promoter operably linked to the insert (see vector map). Wherein, the plasmids may be administered intravenously (Examples 10 and 11, col. 47, 48).

Based on the guidance provided by Hogan et al. on a method of administering vaccinia virus encoded IL-12 to mice sensitized with antigen to reduce allergic lung inflammation the teachings of Li et al. on a method of administering plasmid encoded IFN- γ to mice sensitized with antigen to reduce allergic lung inflammation and the teachings of Dow et al. on the use of plasmids encoding IL-12 or IFN- γ to reduce allergic inflammation, it would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Hogan et al. with the guidance of Li et al. by administering vaccinia viral or plasmid vectors separately encoding IL-12 and IFN- γ .

A practitioner in the art would be motivated to administer vectors encoding IL-12 and IFN- γ in order to increase serum IFN- γ levels above those produced by vector encoded IFN- γ or IL-12 alone thereby decreasing the eosinophils and levels of IL-4 and IL-5 cytokines, and producing better protection against allergic inflammation, such as lung inflammation.

The person of ordinary skill in the art would have a reasonable expectation of success because the administration of two vectors separately encoding IL-12 and IFN- γ would have been a minor and routine modification to the method of Hogan et al.

Response to Arguments

Applicant's arguments filed 7/15/2005 have been fully considered but they are not persuasive. Applicant argues that the cited references do not provide a reasonable expectation of

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increasing TH-1 type cytokine production and decreasing TH2-type cytokine production.

However as previously stated. , Hogan teaches that in mice sensitized with OVA (pg. 420,

Section 4.2), IL-12 gene delivery inhibits airway inflammation (pg. 415, Figure 1, Col. 1),

increases the levels of IFN- γ and decreases the levels of IL-4 and IL-5 expressed in lung cells

(pg. 416, Figure 2) after administration in gelatin saline (pg. 420, Section 4.7). Hogan et al.

teaches that IL-12 protects against lung damage by increasing the levels of IFN- γ expressed (pg.

418, col.1). IFN- γ is a TH-1 cytokine and IL-4 and IL-5 are TH-2 cytokines. Further, applicant

argues that applicants have shown an unexpected synergistic shift that was greater than would be

expected from the additive effects of IL-12 and IFN- γ individually. However, applicant has not

indicated why the skilled practitioner would not expect that IL-12 and IFN- γ would interact to

produce a synergistic effect given that Hogan et al teaches that IL-12 upregulates ILN- γ

production, which is vital for protection from allergic airways disease. This suggests that the two

cytokines have complex interactions/regulatory roles that are more likely to be synergistic than

additive in effect.

Claims 2,3,6,8,12,21,23,24,26,29,50, and 57 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Kumar et al. {Kumar et al. (2001) J. Allergy Clin Immunol; 108:402-8}, further in view of Hogan et al. {Hogan et al. (1998) Eur. J. Immunol. 28: 413-423}, Carroll et al. {Carroll et al. (1998) J. of the Nat. Canc. Inst. 90:1881-1887}, Genbank Accession No: B38957 {Accession No: B38957, now gi: 1082578 (12.01.2000), Genbank Accession No: X13274 {Accession No: X13274 (11.15.1994)}, US Patent Application No: 2003/0138404

(7.24.2003), priority to (7.14.1995), and European Patent Application No. EP343388A2 (11.29.1989). This new rejection is necessitated by applicant's amendments to the claims.

Applicant should note that the inventors of the present application authored the reference of Kumar et al., however Aruna K. Behera, Jianan Hu and Richard F. Lockey, who are not listed as inventors on the instant application, also authored the reference of Kumar et al.

Kumar et al. provides guidance on the administration of plasmids encoding the cytokines IL-12 and IFN- γ to increase the effectiveness of allergen vaccines (Abstract). Wherein one plasmid encodes both the mouse p35 subunit and the mouse p40 subunit, each under the control of a separate CMV promoter and the second plasmid encodes mouse IFN- γ (pg. 403, col.1). Kumar et al. teaches that the plasmids are administered together via intramuscular injection to the mice, along with a subcutaneous injection of Kentucky bluegrass extract. Wherein, mice vaccinated with the plasmids had lower levels of IgE and higher levels of grass allergen specific IgG2a in comparison with control mice (Abstract). Further, Kumar et al. teaches that the vaccination with the plasmids increased the production of TH-1 type cytokines, such as IL-2, and decreased production of IL-4 cytokines such as IL-4 (Abstract; pg. 405, Figure 3). These changes prevented the development of airway hyper-responsiveness (pg. 405, col 2). Finally, Kumar et al. teaches that delivering plasmids encoding IL-12 and IFN- γ together is more effective at inducing a protective airway response than delivering them alone. Kumar et al. does not teach the administration of the nucleic acids encoding IL-12 and IFN- γ comprised within a viral vector. Finally, Kumar et al. does not teach the administration of plasmids comprising SEQ ID Nos: 7,9, or 11; nor does Kumar teach the administration of plasmids encoding SEQ ID Nos: 8,10, or 12.

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Hogan et al. supplements Kumar et al. by providing guidance on the construction and administration of a vaccinia virus encoding the p35 subunit and the p40 subunit of mouse IL-12 operably linked to a promoter (pg. 420, Section 4.7). Said sequences are biologically equivalent to SEQ ID NOs: 7 & 8 (human p35 subunit) and SEQ ID Nos: 9 & 10 (human p40 subunit). Further, Hogan teaches that in mice sensitized with OVA (pg. 420, Section 4.2), IL-12 gene delivery inhibits airway inflammation (pg. 415, Figure 1, Col. 1), increases the levels of IFN- γ and decreases the levels of IL-4 and IL-5 expressed in lung cells (pg. 416, Figure 2) after administration in gelatin saline (pg. 420, Section 4.7). Hogan et al. teaches that IL-12 protects against lung damage by increasing the levels of IFN- γ expressed (pg. 418, col.1). Finally, Hogan et al teaches that viral titers in the mouse lung peaked at day 3 after administration of vaccinia encoded IL-12 (pg. 417, Figure 4), which indicates that the viral nucleic acid was contained within a cell.

Carroll et al. supplements Kumar et al. by providing guidance on the construction of a vaccinia virus that expresses IL-12 and an additional immunostimulatory molecule (Abstract, pg. 1882, col. 1, Materials and Methods). Carroll et al. teaches that the “vaccinia virus is well-characterized expression vector that has been used to express a wide variety of recombinant proteins” (1881, col. 1).

Genbank Accession No: B38957 supplements Kumar et al. by providing guidance on a sequence identical to SEQ ID NO: 8, which is the amino acid sequence of the human IL-12 p35 subunit.

Genbank Accession No: X13274 supplements Kumar et al. by providing guidance on a sequence identical to SEQ ID NO: 10, which is the amino acid sequence of the human IL-12 p40 subunit.

US Patent Application No: 2003/0138404 supplements Kumar et al. by providing guidance on sequence 13, which is identical to SEQ ID NO: 11 and encodes human IFN- γ .

European Patent Application No. EP343388A2 supplements Kumar et al. by providing guidance on sequence identical to SEQ ID NO: 12, which is the amino acid sequence of the human IFN- γ .

Based on the guidance provided by Kumar et al. on a method of administering plasmids encoding the cytokines IL-12 and IFN- γ to increase the effectiveness of allergen vaccines, the guidance of Hogan et al. on the administration of a vaccinia virus encoded IL-12 to mice sensitized with antigen to reduce allergic lung inflammation and the teachings of Carroll et al. that vaccinia viruses can be used to encode multiple immunostimulatory proteins, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Kumar et al. by constructing a vaccinia viral vector that contained the nucleic acid sequences of both IL-12 and IFN- γ , along with CMV promoter sequences. Further, based on the guidance of Kumar et al. on a method of administering plasmids encoding the cytokines IL-12 and IFN- γ to increase the effectiveness of allergen vaccines and the teachings of Genbank Accession No: B38957, Genbank Accession No: X13274, US Patent Application No: 2003/0138404, and European Patent Application No. EP343388A2, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Kumar et al. by constructing plasmids encoding the human

IL-12 p35 subunit (SEQ ID NO: 8), the human IL-12 p40 subunit (SEQ ID NO: 10), and human IFN- γ (SEQ ID NO: 12) using a nucleic acid sequence such as SEQ ID NO: 11.

A practitioner in the art would have been motivated to construct a vaccinia vector containing nucleic acids encoding IL-12 and IFN- γ in order to increase transfection efficiency and the effectiveness of allergen vaccines.

A practitioner in the art would have been motivated to construct plasmids encoding human IL-12 and IFN- γ in order to increase effectiveness of allergen vaccines in humans without the danger of inducing immune responses to mouse IL-12 and IFN- γ . The practitioner would be motivated to use nucleic acid sequences encoding SEQ ID NO: 8, 10 and 12 since these protein sequences were well known in the art at the time of filing. More particularly, the practitioner would have been motivated to use the nucleic acid sequence of SEQ ID NO: 11 because it was known successfully encode human IFN- γ for expression *in vivo*.

A practitioner in the art in the art would have a reasonable expectation of success because the construction of a vaccinia virus encoding IL-12 and IFN- γ , or the construction of plasmids encoding SEQ ID NO: 8, 10 and 12, comprises a minor modification to the methods taught by Kumar et al that would have been routine in the art at the time of filing.

No Claims Allowed

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days.

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